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REVIEW PAPER OPEN ACCESS

Impact of endosulfan on living beings

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Abstract

Endosulfan is a globally used pesticide which causes a great threat to the balance of the environment. It comes under the organochlorine group which is mainly hazardous for the existence of life, during its whole run from the time of spraying till its degradation. It has two isomers, alpha and beta. Both will be degraded into different substrates, among which endosulfan sulfate is more toxic compared to others. Its extensive use throughout the world has made it a hazardous chemical to human beings, which has become the reason for its ban in most of the countries. This article is totally based on literature survey. In this review chemical nature of this pesticide and its application and use has been discussed. The author explored the toxicity of this pesticide. The effects of endosulphan on the aquatic life as well as on humans were also discussed. Moreover focus has been made on the effect of endosulfan on ovary, hormones, enzymes, DNA damage and apoptosis. The effect of this pesticide on oxidative stress and its biodegradation were also explained. This review will be useful for the researchers working in the field of pesticides and will create an awareness regarding its hazardous effect.

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Introduction

Organochlorine pesticides are being extensively used in agriculture and disease control purposes for the last more than fifty years worldwide and their long persistence in soil have been reported. This pesticide residue is capable to affect the soil fertility, crop productivity, ecological imbalance and caused human health problems (Verma *et al.*, 2011). In developing countries such as India where the economy depends largely on agricultural products, one cannot afford to loose the harvest to pests. In India, fifteen to twenty percentage of the total harvest is destroyed by pests resulting in uncontrolled use of pesticides by the Indian cultivators. Endosulfan is a widely used insecticide in India to maintain crops and food productions, fight against infecting pests, safeguard humans from vector borne diseases and related epidemics (Ayub *et al.*, 2003). However, this pesticide has significant toxicity to non-target organisms including humans. The major routes of exposure to these chemicals are through food chain series, dermal contact, respiratory tract etc. The workers in the field and those involved in the application of these insecticides are at high risk of toxicity manifestations by these chemicals (Ayub, 2003).

This review article is totally based on literature survey. In this article the author described various harmful aspects related with endosulfan toxicity. The author reviewed the literature at a massive level and presented this article in concise and condensed form. In this article the author focused on the chemical nature of this pesticide and its applications in different parts of the world. Much attention has been made on the toxicity of this pesticide. Moreover the author also surveyed the effect of endosulfan on the aquatic life as well as on humans. Much focus has been made on the effect of endosulfan on ovary, hormones, enzymes, DNA damage and apoptosis. The author also described the effect of this pesticide on oxidative stress and also about its biodegradation. The aim of review is to create the awareness of this hazardous chemical in the mind of researchers as well as the reader of this article. This will make them to arrange an alternative to this pesticide reducing its hazardous effect on lives.

Chemical nature of endosulfan

Endosulfan is an organochlorine insecticide belonging to the cyclodiene group that is extensively applied in agriculture to protect crops (Li *et al.*, 2009) It is sold under the trade name of Thiodan® which is a mixture of 70% endosulfan-α (endosulfan I) and 30% endosulfan-β (endosulfan II) (Richard et al., 2010). The technical grade endosulfan (1,2,3,4,7,7-hexachlorobicyclo-2,2,1-heptene-2,3-bishydroxy methane-5,6-sulfite) is a mixture of two stereoisomers, a α- and β-endosulfan, in the ratio of 7:3. It is extensively used throughout the world to control the pests on different crops (Verma *et al.*, 2011).

Endosulfan and its application

Endosulfan is a broad-spectrum cyclodiene insecticide that has been used extensively for a longer period of time on a variety of crops (Li *et al.*, 2009). Creatures affected by endosulfan have been listed in the Table 1. This chemical has been used in many countries and has been summarized in the Table 2. This pesticide has been banned in many countries; however, it is still used in the United States (Parbhu *et al.*, 2009). It has its effect on flora and fauna. Throughout the world in different countries, endosulfan is used as a pesticide and in so many countries it is banned because of its ill effects. It was a cause of panic in British Columbia, where it has been sprayed since years. Some other issues were reported in countries like Cuba, Benin and India were it is still in use and has produced very dangerous effects such as congenital birth defects, cancer, loss of immunity, neurological and mental disorders, reproductive health problems, etc. Along with this, in so many countries its toxicity was reported (Wan *et al.*, 2005).

Table 1. Effect of endosulfan on biological creatures.

Effect on biological creatures	Nature of effect	References
Tea	Accumulation	Li et al., 2009.
Phytoplankton	Accumulation	Li et al., 2009.
Zooplankton	Accumulation	Li et al., 2009.
Fishes	Accumulation	Li et al., 2009.
Vegetables	Accumulation	Li et al., 2009.

Endosulfan toxicity

The chlorinated pesticides persist in the environment for very long periods, undergo bioaccumulation and biomagnifications and therefore impart toxicity to non-target organisms including human beings (Kumar *et al*., 2008). It is capable of high lethality and significant morbidity. The commonest manifestations are neurological although other organ dysfunction also occurs (Moses and Peter, 2010). Endosulfan poisoning caused the hypotension and the abnormalities on electrocardiogram (Moses and Peter, 2010). Over half of the patients developed complications, such as rhabdomyolysis, hepatic toxicity, and hypotension (Moon and Chun 2009). This insecticide produces convulsions, headache, dizziness and ataxia. It can cause life threatening metabolic disturbances (Satar et al., 2009). Moreover it also causes much intentional and unintentional toxicity in developing countries and also in Turkey (Kucuker *et al*., 2009). It is absorbed from the gastrointestinal tract, skin, and respiratory tract, and leads to nausea, vomiting, paraesthesia, giddiness, convulsion, coma, respiratory failure, and congestive cardiac failure. Hepatic, renal and myocardial toxicity, agranulocytosis, aplastic anemia, cerebral edema, thrombocytopenia, and skin reaction also have been reported (Ramaswamy *et al*., 2008). Pesticides are capable of affecting the enzyme activity. High affinity for thio groups of enzymes and other proteins resulted in endosulfan toxicity (Sammaiah *et al*., 2011). Presence of endosulfan will be transferred from one trophic level to another thus affecting the whole food chain (Lawrence and Isioma., 2010). It can affect the reproductive system of animals and cause reduced sperm production, improper development of penis, cryptorchidism, testicular tumor. Long exposure to endosulfan results in vacuolization of spermatogonia in goat (Sharma *et al*., 2010). System and organ affected by this pesticide has been listed in the table 3 and toxicity caused by this chemical has been listed in table 4.

Effect on aquatic life

Endosulfan affects the aquatic environment. Some of the changes taking place in their life style is reported throughout the world (Menon *et al*., 2008). In adrenocortico cells of rainbow trout, according to doses it directly affects the cell viability and cAMP secretion (Bisson and Hontela, 2002). Very little dose of it is lethal to the fresh water microfauna like *Mesocyclops leuckarti* and other plank tonic organisms (Kurve and Kulkarni, 2003). Higher exposure to it can change the hepatic metabolism of fish like hepatic somatic index, smaller values of liver weight, histopathological and ultra structural alterations. No significant alteration was observed in the cholinesterase activity of brain and striated muscle (Balasubramani and Pandian., 2008). This particularly result in restlessness, hyperactivity, irritation, difficulty in respiration as it moves to the surface to gulp air, rapid body movement, darkening of the color, loss of equilibrium by swimming sideways and finally collapse and death occurred because of transfer of toxicity to nervous system (Kenneth and Willem., 2010). Endosulfan acted as a growth suppressant, with the magnitude of its suppression in Zebra fish, in the order of female > male > juveniles. It affected sexual maturity in females, reduced the spawning frequency and cumulative fecundity by affecting the processes of egg maturation and vitellogenesis. It also affected males by postponing sexual maturity and reducing fertilizability by reducing the motility duration of the sperm (Relyea., 2009). Its low concentrations can be highly toxic to amphibians and has been suggested that this mortality may exhibit important lag effects. Its effect was dose as well as phylogenetically dependent (Jones *et al*., 2009). In case of amphibians, there was

an apparent direct toxic effect of endosulfan that caused 84% mortality of leopard frogs. Wetland communities can be dramatically impacted by low concentration of endosulfan (Shegefti *et al*., 2010). It is one of the predominant pesticides in the arctic environment which is seen in the blubber of marine mammals. It also biomagnifies the arctic marine food web leading to drastic effects on marine ecosystem (Muir and Wit, 2010). Largely alpha-endosulfan accumulates in the food chain causing a great threat to human health and global environment (Aful *et al*., 2010).

Effect on human

Endosulfan comes under group 1 pesticides which causes physiochemical changes in human body. In women it is found in fatty tissue, human milk, placenta and umbilical cord. Among all, higher concentration is present in adipose tissue followed by human milk (Cerrillo *et al*., 2005). Endosulfan is endocrine-disrupting compound which can enter into the body through different modes. It could change the mechanism of MAPKinase signaling which lead to changes in survival, growth and proliferation of epithelial cell resulting in cancer (Ledirac *et al*., 2005). Sometimes it induces reactive oxygen species production in human liver which can induce apoptosis in T cells (Ledirac *et al*., 2005). It causes congenital cryptorchidism in human (Damgaard *et al*., 2006). Longer exposure to it sometimes gives rise to permanent neurological disorders which directly affects the central nervous system (Kang *et al*., 2001). It could transduce the overstimulation of number of symptoms like confusion, headache, agitation, diarrhoea, vomiting, nausea, oedema, blood pressure and pulse rate, respiratory rate and changes in some biochemical parameters (Karatas *et al*., 2006). With proper management its poisonous effect can be cured (Karatas *et al*., 2006).

Table 2. Countries which showed the contamination by endosulfan or its compound.

Country	Contamination rate or frequency	References
China	Detection frequency of alpha endosulfan and gamma endosulphan in agriculture soil of Shanghai was 47% and 25% respectively.	Li *et al*., 2011; Jiang *et al*., 2009.
Pakistan	Percentage contamination of farmer with endosulfan was 27% .	Memon *et al*., 2011: Khan *et al*., 2010; Khan *et al*., 2008.
Korea	Percentage of patient died due to endosulfan poisoning was 30.7%.	Park *et al*., 2010; Moon and Chun, 2009.
Indonesia	Endosulphan was found in the milk of Indonesian women.	Burke *et al*., 2003
South Florida	Potential chronic risk (9.2% for total endosulfan) was reported.	Rand *et al*., 2010.
USA	Endosulfan at a concentration of 0.11 to 1.2 microg/kg was found in surface sediments and in snow.	Menone *et al*., 2008; Mast *et a*l., 2007.
India	Ground water exhibit contamination rate with beta-endosulfan ranging between 0.21 and 0.87 microg L(-1) and also with alpha-endosulfan ranging between 1.34 and 2.14 microg L(-1). In Ganga river the concentration found was 66.5µg/L	Pandey *et al*., 2010; Shukla *et al*., 2006. Menone *et al*., 2008.
Argentina	Beta-endosulfan concentrations up to 318 and 43 microg/kg were measured from suspended-particle samples from Horqueta and Helves respectively.	Menone *et al*., 2008; Jergentz *et al*., 2004.

Table 3. System and organ effected by endosulfan.

System effected by endosulfan	Nature or type of abnormalities	References
Central nervous system	Syncope, Excitation, and Convulsions.	Li *et al.*, 2009; Moon and Chun, 2009.
Liver	Microscopic hepatic lesions, swellon and pale livers.	Li *et al.*, 2009; Benjamin *et al.*, 2006; Mor and Ozmen, 2010.
Kidney	Tubular dilation, hydropic degeneration in tubular epithelium, hemorrhage in the cortical and medulla part of the kidney.	Li *et al.*, 2009; Kayhan *et al.*, 2009.
Blood	Effect blood biochemistry and hematological values.	Li *et al.*, 2009; Hatipoglu *et al.*, 2009.
Parathyroid gland	Parathyroid hyperplasia.	Li *et al.*, 2009; Reuber, 1981.

Humans are exposed to the endosulfan by the skin contact, through smoking or via contaminated food. Endosulfan susceptible people include the unborn and neonates, the elderly and people with liver, kidney, immunological, hematological or neurological disease. Human glial and neuronal cells were most sensitive to endosulfan toxicity. Humans may develop some neurological diseases induced by it, and nerve cells once damaged could not be regenerated (Chan et al., 2007). Along with the estrogenic effect it also affects the thyroid gland. The nerve cell receptor which actually helps in brain development, when bound to endosulfan results in autism spectrum disorder (Roberts *et al.*, 2007). By statistical analysis it was observed that the long exposure to endosulfan could result in genotoxic effect. It was also concluded that it could lead to mental retardation and bone marrow cancer due to its neurotoxic and immunotoxic effects. It has also been identified from cord blood sample during delivery, in human sera and also in mother breast milk (Cerrillo *et al.*, 2005). Another effect which was shown at cytogenetic level was that it could do chromosome aberration per cell (Saraswathy et al., 2011). It has its effect on immune system, ovary and also on hormones and enzymes.

Effect on immune system

Endosulfan is a widely used insecticide with immunosuppressive or immunopotentiating effects which alters the immune response of fish. Phagocytosis, increased significantly in exposed fish to endosulfan (Tellez-Bañuelos *et al.*, 2009). Short exposure to low concentration of endosulfan stimulated macrophage activity. Spleen cell viability and relative spleen weight were lower in exposed organisms compared to non-exposed ones, without reaching statistical significance. (Tellez-Bañuelos *et al.*, 2009). It is known to induce immunological alterations in juvenile Nile tilapia (*Oreochromis niloticus*) such as increases in phagocytic activity and reactive oxygen species production of spleen macrophages (Tellez-Bañuelos *et al.*, 2010). Endosulfan exposure triggers a succession of events beginning with non-specific activation of macrophages followed by an exacerbated synthesis of the IL-2L factor by activated B cells. This leads to significantly increased secretion of IgM and could in turn facilitate autoantibody production and the development of autoimmune pathologies (Tellez-Bañuelos *et al.*, 2010). Perturbations in immune responses induced by concurrent subchronic exposure to arsenic and endosulfan were also reported (Aggarwal *et al.*, 2008). Moreover reports were also made on inflammatory effect of endosulfan via NF-κB activation in macrophages (Han *et al.*, 2007).

Effect on ovary

Effect of endosulfan on ovarian compensatory hypertrophy in hemicastrated albino mice was reported (Hiremath and Kaliwal. 2002). Endosulfan treatment caused a significant decrease in compensatory ovarian hypertrophy. An increase in the number of atretic follicles and disruption of the estrous cycle may have been due to a direct effect on the ovary or to effect on the hypothalamo–hypophysial-ovarian axis (Hiremath and Kaliwal, 2002). Endosulfan affects buffalo oocyte maturation, fertilization, and embryo development *in vitro* directly and through cumulus cells (Nandi *et al*., 2011). Dose-dependent effects of endosulfan and malathion on adult Wistar albino rat ovaries were also evaluated (Koc *et al*., 2009). Non-breeding females mosquito fish exposed to endosulfan had a significantly greater ratio of anal fin/ body length and larger thyroid follicles than did control females (Park *et al*., 2004).

Table 4. Toxicity caused by endosulfan in mammals.

Toxicity caused by endosulphan	Reference
Neurotoxicity	Chaudhiri et al., 1999.
Renal toxicity	Chaudhiri et al., 1999.
Hepatotoxicity	Chaudhiri et al., 1999.
Haematological toxicity	Chaudhiri et al., 1999.
Respiratory toxicity	Chaudhiri et al., 1999.
Reproductive toxicity	Chaudhiri et al., 1999.
Gonadal toxicity	Singh and Pandey, 1990.
Genotoxicity	Chaudhuri et al., 1999.

Effect on hormones and enzymes

Endosulfan effects on pituitary hormone and both nitrosative and oxidative stress in pubertal male rats. In the pituitary gland, endosulfan has been shown to mediate their actions via voltage-dependent L-type Ca2+ channels, and is able to alter expression and secretion of pituitary hormones, as prolactin, luteinizing hormone and thyroid stimulating hormone (Caride *et al*., 2010). This pesticide significantly increased the level of lactate dehydrogenase in rats (Jaiswal *et al*., 2005). Dietary exposure of Nile tilapia to endosulfan can lead to changes in circulating thyroid hormone levels and/or in peripheral thyroid hormone metabolism. The changes in hormone metabolism differ between tissues, eventually reflecting tissue-specific differences in adaptation (Coimbra et al., 2005). Male children exposed to endosulfan may delay sexual maturity and interfere with sex hormone synthesis (Saiyed *et al*., 2003). It has been demonstrated to induce hepatic P450 biotransformation enzymes (Wilson and LeBlanc, 1998). Increases in testosterone biotransformation from endosulfan exposure can result in increases in the elimination of the steroid (Wilson and LeBlanc, 1998). Effect of endosulfan (thiodan) on vitellogenesis and its modulation by different hormones in the vitellogenic catfish (*Clarias batrachus*) was also reported (Chakravorty *et al*., 1992).

DNA damage and apoptosis

Endosulfan is a synthetic chlorinated and environmental genotoxic pesticide used worldwide for crop production (Lajmanovich *et al*., 2005). This pesticide has been reported for having the potential genotoxicity for HepG2 cell line by inducing DNA damage (Li *et al*., 2011). The mixture of pesticides namely endosulfan, chlorpyriphos and thiram have been reported to cause DNA damage (Topè and Rogers, 2009). Endosulfan induced DNA damage in earthworm and white clover nuclei were also described (Liu *et al*., 2009). Studies were also made on the genotoxicity of endosulfan in different tissues of fresh water fish using the comet assay (Sharma *et al*., 2007). DNA damage and mutagenicity induced by endosulfan and its metabolites were also studied (Bajpayee *et al*., 2006). Alpha-endosulfan and ss-endosulfan are isomers of endosulfan, a pesticide used worldwide both [alpha]- and ss-endosulfan are genotoxic to HepG2 cells and that the genotoxicity of ss-endosulfan seems stronger than that of [alpha]-endosulfan (Lu *et al*., 2000). Endosulfan also induced a dose-dependent increase in forward mutations in *E. coli K12* cells from ampicillin sensitivity to ampicillin resistance

(Chaudhuri *et al*., 1999). This pesticide can induce apoptosis in a human T-cell leukemic cell line which may have direct relevance to loss of T cells and thymocytes *in vivo* (Kannan *et al*., 2000).

Endosulpfan and gene expression

Endosulfan has affects on vertebrate xenobiotic metabolism pathways that may be mediated, in part, by its ability to activate the pregnane X receptor and/or the constitutive androstane receptor which can increase expression of cytochrome P450 (CYP) enzymes. This study examined the dose-dependency and receptor specificity of CYP induction *in vitro* and *in vivo* (Richard *et al*., 2010). Expression and inducibility of endosulfan metabolizing gene in *Rhodococcus* strain isolated from earthworm gut microflora for its application in bioremediation was also reported (Verma *et al*., 2011).

Endosulfan and oxidative stress

Endosulfan has been reported as an oxidant creating oxidative stress (Saxena *et al*., 2011). Endosulfan induced cell membrane damage of the hepatocytes by increasing the leakage percentages of LDH, ALT, AST and gamma-GT have been reported (El-Shenawy, 2010). The activities of the antioxidant enzymes like superoxide dismutase, glutathione peroxidase and glutathione-S-transferase were reported to be decreased by endosulfan (El-Shenawy, 2010). The activities of the antioxidative enzymes and the antioxidant contents such as the super oxide dismutase, peroxidase, ascorbic acid and total phenols increased with increase in the concentrations of endosulfan in different parts of the plants in *Cajanus cajan* (Mathad and Siddaling, 2009). Activation of spleen macrophages and a decrease of catalase activity have been observed after endosulfan exposure in fish (Slaninova *et al*., 2009). Endosulfan exposure to rats significantly decreased the activities of superoxide dismutase and catalase, level of reduced glutathione and increased lipid peroxidation (Pal *et al*., 2009). The cytotoxic action of the pesticides on the cells were characterized by glutathione depletion, induction of reactive oxygen species. The cell death induced by the pesticides was of necrotic type as confirmed by lactate dehydrogenase leakage (Rana and Shivanandappa, 2010). Endosulfan also induces oxidative stress and changes on detoxication enzymes in the aquatic macrophyte *Myriophyllum quitense* (Menon *et al*., 2008).

Biodegradation of endosulfan

Endosulfan gets sorbed to soil and sediments owing to its hydrophobic nature. This makes it persistent in soil and sediments (Tejomyee *et al*., 2007). Degradation of endosulfan through biological means is receiving serious attention as compared to existing methods such as incineration and landfill. In biodegradation progress, heterotrophic microorganisms break down substrates (hazardous compound) to obtain chemical energy, hence organic pollutants can serve as carbon, energy, and nutrient sources for microbial growth (Siddique *et al*., 2003). In biodegradation, endosulfan can be degraded by attacking the sulfite group via either oxidation to form the toxic metabolite endosulfan sulfate or hydrolyse to form the less toxic metabolite endosulfan diol. Endosulfan diol is a non-toxic metabolite to fish and other organisms. It can be further degraded to non-toxic endosulfan ether, endosulfan hydroxyether and endosulfan lactone; thus, production of endosulfan diol via hydrolysis may be an important detoxification pathway of endosulfan (Li *et al*., 2009). Biodegradation and detoxification of endosulfan in aqueous medium and soil by *Achromobacter xylosoxidans* strain CS5 was reported (Li *et al*., 2009).

Klebsiella oxytoca, *Bacillus spp*., *Pandoraea sp*., and *Micrococcus sp*. are the bacteria reported to degrade endosulfan in solutions and soils (Kwon *et al*., 2005; Awasthi *et al*., 2003; Guha *et al*., 2000). Many fungi have been tested for their ability to degrade endosulfan, including *Aspergillus niger*, *Aspergillus terreus*, *Cladosporium oxysporum*, *Mucor*

thermohyalospora, *Fusarium ventricosum*, *Phanerochaete chrysosporium*, *Trichoderma harzianum*. *Anabaena sp*., *Chlorococcum sp*., and *Scenedesmus sp*., are the photosynthetic microorganisms applied in endosulfan degradation studies (Tejomyee *et al*., 2007). Endosulfan degradation by a Rhodococcus strain isolated from earthworm gut was reported (Verma *et al*., 2006). *Klebsiella pneumoniae* KE-1 degrades endosulfan without formation of the toxic metabolite, endosulfan sulfate (Kwon *et al*., 2002).

Conclusion

The use of pesticide along with irrigation, fertilization and mechanization reduces the damage done to crops and maintains food production in order to feed the growing population. High yield of crops give economic benefits and betterment. Nearly 90% of the pesticides applied to the agricultural land never reach the desired targets and as a result this accidentally affects many organisms sharing the same environment as pests. Among so many pesticides, endosulfan is the largely used one because of its characteristic features.

Endosulfan, though used for betterment of mankind, has ultimately resulted in being dangerous to environment. The toxic residues of it impairs the development and normal functioning of the hormone-dependent processes in flora, fauna and has lead to severe and chronic human poisoning. It has been banned in many developed countries. Ban of endosulfan in India is in consideration, as it leads to many drastic effects, resulting in death. It is the requirement of the present time to reduce the ill effect of this pesticide. Government must come forward with an alternative to reduce the hazardous effect of this pesticide strictly or stop its future use completely.

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